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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,628	05/09/2005	Peter Hegemann	231181	4179

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EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,628	HEGEMANN ET AL.	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2008 and 12 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-26 and 32-35* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,10,19-26 and 32-35* is/are rejected.

7)☒ Claim(s) *8,11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kimberly Ballard, Art Unit 1649.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on January 12, 2009 has been entered.

Status of Application, Amendments, and/or Claims

3. Claims 1, 8, 21, 22, 25, 26 and 35 have been amended as requested in the amendment filed November 6, 2008. Following the amendment, claims 1-5, 8-26 and 32-35 are pending in the present application. Claims 13-18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in the response filed on November 1, 2007.

Accordingly, claims **1-5, 8-12, 19-26**, and **32-35** are under examination in the current office action.

Withdrawn Objections or Claim Rejections

4. The objection to claim 8, regarding sequence compliance requirements of 37 CFR 1.821 through 1.825, as set forth at paragraph 4 of the previous office action (05/07/2008), is withdrawn in view of Applicants' amendment to the claim.

5. The rejection of claims 1-5, 8-12, 19-26 and 32-35 under 35 U.S.C. 112, second paragraph, as set forth at paragraphs 6-11 of the previous office action (05/07/2008), is withdrawn in view of Applicants' amendments to the claims.

6. The rejection of claims 1-5, 19-23 and 32 under 35 U.S.C. 102(b) as being anticipated by Hildebrandt et al. (1993), as set forth at paragraphs 13-15 of the previous office action (05/07/2008), is withdrawn in view of Applicants' arguments.

7. Applicants' submission of a certified English translation of the German patent application to which the present application claims to priority under 35 U.S.C. § 119 is sufficient to overcome the 102(a) rejection of claims 1-5, 8-12, 19-22 and 35 as anticipated by Nagel et al. (June 2002). The certified English translation of the foreign priority papers (DE 102 16 005.8) has been made of record.

New Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for increasing or decreasing the ion conductivity of a membrane, comprising inserting one or more light-controlled ion channels into a membrane, wherein the channel is a biological photoreceptor and comprises an apoprotein and a light-sensitive polyene covalently bound to the apoprotein, wherein the apoprotein is derived from lower plants (claim 9) and wherein the lower plants are algae (claim 10). Thus, the claims are drawn to a method of using a genus of apoprotein molecules derived from the kingdom of lower plants such as algae, and are therefore considered genus claims. The word "derived" implies that structural changes can be made to naturally occurring lower plant sequences, and the resulting derivative is still encompassed by the claim.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to

be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims is the functional characteristic of the apoprotein (capable of light-controlled ion transport) and the recitation that the apoprotein is "derived from" lower plants, such as algae. There are no explicit structural requirements for the apoprotein present in claims 9 or 10, and the specification teaches only that an apoprotein is a membrane protein with at least 5 transmembrane helices and is capable of binding a light-sensitive polyene (page 3). The specification discloses two specific apoproteins derived from the motile green algae *Chlamydomonas reinhardtii*, Channelopsin1 (CHOP-1) and Channelopsin2 (CHOP-2), and considers the use of opsins from other green algae in the division of Chlorophyceae, as well as apoproteins from Volvocales and Ulvophytes such as *Acetabularia* and *Ulva*, members of Prasinophyceae such as *Pyramimonas* and *Platymonas (Tetraselmis)*, and members of Dinophyceae such as the species of *Gymnodinium splendens, Gyrodinium dorsum, Peridinium balticum* and *Gonyaulax* (page 7). However, not including brown or red algae (which would be encompassed by the broad recitation of "algae" in claim 10), there are over 3,800 species of green algae under Chlorphyceae and between 4,000-6,000 species of green algae under Charophyceae (see Wikipedia entry for "Plant" retrieved on 03/18/2009). Furthermore, a reasonable interpretation of the claim includes structurally modified forms of lower plant proteins, and thus the claims encompass an infinite number of possible structures. Therefore, the limited examples of CHOP-1 and CHOP-2 from

Chlamydomonas reinhardtii do not provide sufficient evidence of the broad genus of apoprotein molecules potentially obtainable and derivable from the huge category of "lower plants" and "algae" instantly claimed, especially since it is not known whether any other the other algal species possess apoproteins that would be consistent with use within the claimed method. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the apoproteins CHOP-1 and CHOP-2 derived from *Chlamydomonas reinhardtii*, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods comprising the use of apoproteins derived from *Chlamydomonas reinhardtii* (i.e., the CHOP-1 protein (SEQ ID NO: 1) or the CHOP-2 protein (SEQ ID NO: 2)), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention wherein the recited apoprotein is obtained from a lower plant, does not reasonably provide enablement for the claimed invention wherein the recited apoprotein is "derived from" lower plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative

skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are directed to a method for increasing or decreasing the ion conductivity of a membrane, comprising inserting one or more light-controlled ion channels into a membrane, wherein the channel is a biological photoreceptor and comprises an apoprotein and a light-sensitive polyene covalently bound to the apoprotein, wherein the apoprotein is derived from lower plants (claim 9) and wherein the lower plants are algae (claim 10). The word "derived" implies that structural changes can be made to naturally occurring lower plant sequences, and the resulting derivative is still encompassed by the claim.

The claims therefore require the use of an extremely broad genus of derived (i.e., modified) protein molecules and, as stated *supra*, Applicants have not described all of the common features of the genus such that the skilled artisan could identify individual members. Applicants have not provided sufficient guidance, for example indicating which (if any) residues within an apoprotein can be modified without loss of function, to allow one of skill in the art to practice the claimed invention with any apoprotein derived a lower plant species. There are no working examples involving the use of modified apoproteins from *Chlamydomonas reinhardtii* other any other algae species as claimed.

The potential amino acid sequences encompassed by the claimed apoproteins have particular structures, the predictability of which is complex and outside the realm of routine experimentation. For example, it is known that a change of two amino acid residues in a protein results in switching the binding of the protein from one receptor to

another (Yan et al. *Science*, 2000, 290(5491):523-527). And Han et al. (*Biochemistry*, 1998; 37:8253-8261) demonstrate that a single amino acid substitution in the rhodopsin molecule at methionine 257 significantly affects the subsequent activity of the rhodopsin mutants. Since detailed information regarding the structural requirements of the numerous potential amino acid sequences encompassed by the claimed derived apoprotein molecules is lacking, and given the lack of working examples evidencing any of the potential modified apoproteins encompassed by the claims, it is unpredictable as to which derivations, if any, meet the limitations of the claims. As such, testing such derived apoprotein molecules for the claimed biological activity would constitute undue experimentation.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to practice the claimed invention with the plurality of derived apoprotein molecules encompassed by the claims, the absence of working examples directed to same, the state of the prior art which established the unpredictability of the claims, and the breadth of the claims, undue experimentation would be required of the

skilled artisan to practice the invention commensurate in scope with the claimed method.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-4, 19-22, 24-26, 33 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 7,144,733 B2 to Miesenböck et al. (issued December 5, 2006, priority to December 31, 2001 and August 16, 2001).

The claims are drawn to a method for increasing or decreasing the ion conductivity of a membrane, comprising inserting one or more light-controlled ion channels into a membrane, wherein the light-controlled ion channel is a biological photoreceptor, and wherein the channel comprises an apoprotein and a light-sensitive polyene covalently bound to the apoprotein, said polyene interacting with the apoprotein and functioning as a light-sensitive gate, thereby increasing or decreasing the ion conductivity of the membrane. Dependent limitations recite that the apoprotein is a

transmembrane protein with 5 or more transmembrane helices (claim 2), the apoprotein is an opsin protein or derivative or fragment of a naturally occurring opsin protein (claim 4), the light-controlled ion channel is a transport system for protons, sodium or calcium (claim 3), the light sensitive polyene is a retinal or retinal derivative (claims 19-20), the proton, sodium or calcium conductivity of a membrane is increased or decreased (claim 21), the membrane potential of a cell membrane is increase or decreased (claim 22), the cell membrane is of a mammalian cell or an insect cell (claim 24), wherein the mammalian cell is a neuron (claim 33), the concentration gradient of ions (protons, sodium, or calcium) across the membrane is raised or lowered (claims 25-26), and the membrane depolarization is realized by lowering the ion conductivity of the membrane by activating one or more light-controlled ion channels by exposure to light (claim 35).

Miesenböck et al. teach a method of sensitizing a cell to light, comprising a) introducing nucleic acids encoding an opsin gene product, an arrestin gene product, and the alpha subunit of a heterotrimeric G protein, such that each gene product is expressed by the cell, b) supplying the cell with retinal or a retinal derivative so as to convert the opsin gene product into a rhodopsin, and c) illuminating the cell with light having a wavelength capable of transforming said rhodopsin into a metarhodopsin whereby said metarhodopsin activates a hetereotrimeric G protein (see column 4, lines 30-43). Miesenböck teaches that metarhodopsin interacts with and activates the heterotrimeric GTP-binding protein, G_q, which through a second messenger cascade and release of calcium ions from intracellular reserves, triggers the opening of cation influx channels TRP (transient receptor potential) and TRPL (transient receptor

potential-like), thereby leading to an influx of cations, such as Na^+ and Ca^{2+}, and resulting in depolarization of the photoreceptor cell (see column 11, lines 3-30). In other words, Miesenböck teaches a method of increasing or decreasing the ion conductivity of a membrane leading to membrane depolarization comprising inserting one or more light-controlled ion channels, wherein the light-controlled ion channel is a biological photorecptor, and the channel comprises an apoprotein (opsin, which has seven transmembrane helices) and a light-sensitive polyene (retinal) as instantly claimed, which would address recited limitations of instant claims 1-4, 21, 22, 25, 26 and 35.

Further, Miesenböck et al. disclose that the preferred cell for this method is a neuron (column 4, lines 19-22), thus anticipating limitations of instant claims 24 and 33. Both retinal and the retinal derivative 3-hydroxyretinal are taught for use in the disclosed methods, which addresses limitations of instant claims 19 and 20. Accordingly, the teachings of Miesenböck et al. anticipate the present invention of claims 1-4, 19-22, 24-26, 33 and 35.

13. Claims 1-4, 19, 21-26, and 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Abdulaev and Ridge (*Methods Enzymology*, 2000; 315:3-11), as evidenced by US Patent No. 7,144,733 B2 to Miesenböck et al., as above.

Abdulaev and Ridge teach the heterologous expression of bovine opsin in the yeast *Pichia pastoris*, and demonstrate that the opsin protein is integrated into the membrane and forms functional rhodopsin and activation of G-protein upon addition of retinal (11-*cis*-retinal) and exposure to light (see Figures 1 and 2, and pp. 7-9).

Abdulaev and Ridge teach that bovine opsin has been successfully expressed in COS-1 and HEK293 cells, *Xenopus laevis* oocytes, baculovirus-infected Sf9 insect cells, wheat germ extracts, and *Saccharomyces cerevisiae* (see p. 3), thus anticipating recited limitations of instant claims 23, 24 and 32-34. The fact that the yeast-expressed opsin is capable of forming a functional unit with the chromophore 11-*cis*-retinal that subsequently catalyzes light-dependent GTPγS binding by G_t is indicative that the opsin expression in *P. pastoris* would inherently be expected to lead to alteration in membrane conductivity, wherein the conductivity of ions (calcium, sodium, or protons) and the ion gradient would be increased or decreased, and membrane depolarization upon exposure to light, as evidenced by Miesenböck et al. The teachings of Abdulaev and Ridge therefore anticipate the invention of present claims 1-4, 19, 21-26 and 32-35.

14. Claims 1-5, 19, 21-22, 24-26, 33 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Han et al. (*Biochemistry*, 1998; 37: 8253-8261), as evidenced by US Patent No. 7,144,733 B2 to Miesenböck et al., as above.

Han et al. disclose the expression of opsin and mutant opsins, wherein an amino acid residue has been exchanged, in COS-1 cell membranes (see Abstract), which would anticipate the limitation of instant claim 5 reciting that the opsin derivative or fragment is the result of an exchange, insertion, or deletion of one or several amino acid(s) in the natural amino acid sequence of the opsin protein. Han teaches that rhodospin has seven transmembrane helices (see Figure 1, p. 8254, which also shows the location of each of the mutated amino acid residues of opsin). The 11-*cis*-retinal

chromophore was added to membrane preparations, thus addressing recited limitations of present claims 1 and 19. The membranes containing the mutated opsins were then assayed for their ability to catalyze GTPγS uptake by G_t under continuous illumination (see p. 8255, 2nd column). Han discloses that 18 of the mutant opsins were significantly constitutively active (see Abstract and Table 1, p. 8255). The light-induced catalytic activity of functionally expressed opsin protein in these membrane preparations is indicative that exposure of these photoreceptors to light would inherently result in the alteration of ion conductivity (such as sodium or calcium), raising or lowering of the concentration gradient of ions, and depolarization of the cell membrane, as evidenced by Miesenböck et al. Accordingly, the teachings of Han et al. anticipate instant claims 1-5, 19, 21-22, 24-26, 33 and 35.

Conclusion

15. Claims 1-5, 9, 10, and 19-26 and 32-35 are rejected. Claims 8, 11 and 12 are objected to as depending from a rejected claim(s), however would be allowable if they were rewritten in independent form including all of the limitations of the independent claim and any intervening claim limitations.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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